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Review

The Use of Transcutaneous Oximetry to Predict Healing Complications of Lower Limb Amputations: A Systematic Review and Meta-analysis

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WHAT THIS PAPER ADDS

- Transcutaneous oximetry ($TcPO_2$) has been proposed as a method to predict healing complications of lower limb amputations and to select appropriate amputation levels. This systematic review and meta-analysis presents the current state of the literature on this topic and pools the relevant observational study results in a meta-analysis. This analysis suggests that $TcPO_2$ predicts healing complications of lower limb amputations, but its independent predictive value has not been determined. The use of $TcPO_2$ may provide surgeons with an important tool for assessing patients for lower limb amputation and for making clinical decisions regarding an appropriate level of amputation.

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ABSTRACT

Objective: To determine the validity of transcutaneous oximetry ($TcPO_2$) as a predictor of lower limb amputation healing complications.
Design: A systematic review and meta-analysis.
Methods: We searched five major medical databases, relevant review articles and reference lists and included all studies that evaluated $TcPO_2$ for its ability to predict lower limb amputation healing failure. We selected eligible articles and conducted data abstraction independently and in duplicate.
Results: Thirty-one studies, enrolling 1824 patients with 1960 amputations, met our inclusion criteria. Only one study reported undertaking a multivariable analysis, which demonstrated that a $TcPO_2$ level below 20 mmHg was an independent predictor of re-amputation occurrence (adjusted odds ratio (OR) 3.08, 95% confidence interval (CI) 1.19–7.98). Fourteen prospective cohort studies reported data that allowed for the calculation of an unadjusted relative risk of lower limb amputation healing complications leading to amputation revision associated with a $TcPO_2$ level below cut-offs of 10 mmHg (1.80; 95% CI 1.19–2.72), 20 mmHg (1.75; 95% CI 1.27–2.40) 30 mmHg (1.41; 95% CI 1.22–1.62) and 40 mmHg (1.24; 95% CI 1.13–1.39).
Conclusions: This review suggests that $TcPO_2$ predicts healing complications of lower limb amputations. A value of less than 40 mmHg results in a 24% increased risk of healing complication compared to over 40 mmHg and the risk further increases as the $TcPO_2$ decreases. There is, however, insufficient evidence to judge whether this tool adds important information beyond clinical data or to suggest an optimal threshold value. There is a need for a large, sufficiently powered study that adjusts for appropriate clinical variables.

The incidence of major lower limb amputations, including below-knee amputation (BKA) and above-knee amputation (AKA), has most recently been reported at 5.1 for every 100,000 people in England.[1] Other studies[2] have cited a much higher rate in North America, especially among Native populations. Feinglass et al.[3] estimated a rate of 25 amputations per 100,000 people in their

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assessment of data from the 1996 National Hospital Discharge Survey. If one considers that approximately 82% of these amputations are a result of vascular complications[4] and that the rate of diabetes is increasing, the number of amputations is expected to increase substantially in the future.

Within the last two decades, there has been a trend towards more distal lower limb amputations. Most recent studies report a BKA:AKA ratio of approximately 2:1.[5–8] This movement has been fuelled by evidence that BKAs improve patients' rehabilitation,[9] mobility,[10] independence, functional capabilities[11] and quality of life.[12] Furthermore, short- and mid-term mortality rates differ significantly between the two procedures: 30-day mortality rates are reported to be between 3.6%[13] and 10.0%[14] for BKAs and between 13.2%[15] and 24.0%[16] for AKAs. Ranges for 1-year mortality rates are 4.3%[17]–25.5%[5] and 24.4%[17]–49.4%[5] for BKAs and AKAs, respectively. Although there is a trend towards more distal lower limb amputations and recent evidence supports the advantages of BKA over AKA, there is still an appropriate hesitancy to adopt BKA for all patients. Failure of the surgical stump to heal postoperatively is more common in BKAs.[7,18] This failure of primary healing often results in the need for revision of the amputation to a more proximal level. Revision of BKA to AKA is required in approximately 14.8% of cases[5,6,16,19] but has been reported at a rate as high as 42.0%.[20] This outcome is associated with not only the decreased ability for rehabilitation and quality of life found in all AKAs, but also the risks of undergoing a second surgery, including general anaesthesia, blood loss, infection and cardiovascular complications.

Current methods to select the level of amputation in patients with critical and chronic ischaemia at many vascular surgery centres are largely clinically based[21] including pallor, erythema, temperature, pulses and the presence of necrosis. Adoption of more specialised measurements for this decision-making process varies by country and is centre-specific. Numerous studies have evaluated these measurements for their predictive value in selecting a more appropriate level of amputation:[12] ankle–brachial pressure index, segmental blood pressures, arteriography,[22] skin blood flow, skin perfusion pressure, laser Doppler flowmetry and thermography. Despite these measures, physicians' abilities to predict surgical wound healing remain suboptimal.

Transcutaneous oximetry ($TcPO_2$), a non-invasive method to analyse the partial pressure of oxygen (PO_2) in tissue, has been proposed as a method to select lower limb amputation levels. This technique uses a sensor containing Clark polarographic electrodes that is placed on the skin at the area of interest, avoiding callous areas, oedema and bony prominences. The sensor warms the surrounding skin, causing localised hyperaemia and facilitating oxygen diffusion. The measured PO_2 in the dermis is displayed in millimetres of mercury, with a normal healthy value in the foot being $>$50 mmHg.[23] A value of $<$40 mmHg is thought to represent sufficient hypoxia to impair wound healing.[23] A cut-off point below which the likelihood of healing complications of amputation stumps is increased is, however, poorly defined.[12] The determination of this cut-off may assist in clinical decision making, as well as guide future research to improve outcomes.

We conducted a systematic review of the medical literature to determine the value of $TcPO_2$ as a predictor of healing complications of lower limb amputation.

Methods

We have followed the Meta-analysis of Observational Studies in Epidemiology (MOOSE) and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement guidelines in the design, conduct and reporting of this systematic review and meta-analysis.

Search strategy

Electronic searches were conducted of the following databases: the Cochrane Library, CINAHL, EMBASE, MEDLINE and Web of Science, using keyword and subject heading searches of terms such as 'amputation' and 'transcutaneous oximetry'. The searches were conducted from the start date of each source to October 2011. The specific search strategy methods for each database are outlined in the Supplementary Data Section (online only). Reference lists of articles that met the eligibility criteria and relevant review articles were hand-searched for additional articles.

Study eligibility

All studies evaluating healing of lower limb amputations for vascular complications in adult patients (age $\geq$ 18 years) were included if they fulfilled the following criteria: conducted at least one preoperative $TcPO_2$ measurement at the site of the planned amputation; reported the postoperative healing status of the surgical wound or rate of amputation revision to a more proximal level; and provided data to assess $TcPO_2$ measurements as a predictor of amputation healing.

Study eligibility was assessed in two stages. First, two individuals independently screened the titles and abstracts of each citation identified in our search. All articles identified as having any possibility of fulfilling our eligibility criteria in the screening process were retrieved to undergo full text evaluation. Two independent reviewers evaluated each full text article selected during the screening stage. In cases of disagreement, the reviewers discussed the reasoning for their decisions and came to a consensus. If disagreements were not resolved during this process, an independent third adjudicator assessed the paper in question and made a final decision. Non-English studies were assessed by third-party translators.

Data collection

Two independent reviewers abstracted the following descriptive data from eligible studies: year of publication, sample size, patient characteristics, length of follow-up, type of amputation, method of amputation level selection, $TcPO_2$ measurements, method of assessment of amputation stump healing and the definition of a non-healing event. Event rates in groups of patients above and below $TcPO_2$ cut-off levels of 10, 20, 30 and 40 mmHg were collected from individual studies where available. Data were abstracted regarding independent associations between $TcPO_2$ and amputation stump healing in studies that undertook multivariable analysis, propensity analysis or matched cases and controls. If a study stated that a type of multivariable analysis was used, but the specific results for a cut-off $TcPO_2$ level were not reported, the authors were contacted for the data.

Study quality assessment

The following indicators of study validity were collected: the method of sample selection, the number of patients lost to follow-up, whether there was blinding of data collectors and outcome assessors to the $TcPO_2$ measurements and whether the assessment method for amputation stump healing was objective and standardised.

Statistical analysis

There were an insufficient number of studies reporting multivariable analysis to perform a meta-analysis and pool the summary estimates of $TcPO_2$ as an independent predictor of amputation stump healing complications. Unadjusted relative risks (RRs) were calculated for each study at each cut-off level. The unadjusted RRs were pooled using the DerSimonian and Laird random-effects model[24] based on the Mantel–Haenszel estimate. This analysis was done using Review Manager (RevMan) Version 5.1 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2011).

To assess heterogeneity, an I^2 value was calculated. Substantial heterogeneity was defined as an I^2 of $\geq$50%. We originally planned to pool the data from all of the studies found in our review. Due to the substantial heterogeneity found, this analysis was deemed inappropriate. Sensitivity analyses demonstrated that much of this heterogeneity was due to variability in study design and outcome definition. Therefore, we pooled only the prospective cohort studies that used the most objective outcome definition: occurrence of amputation revision.

A random-effects meta-regression of the log RR was used to assess the plausible explanatory variables of $TcPO_2$ cut-off value, year of publication and length of patient follow-up. It was hypothesised that decreasing the cut-off value would result in a significantly stronger association of $TcPO_2$ levels below a cut-off with healing failure. It was thought that more recent publications might demonstrate significantly higher summary estimates above 1.00 due to advancements in $TcPO_2$ technology that led to improved measurement accuracy. Finally, increased length of follow-up might capture more events and lead to a weaker association of $TcPO_2$ levels below a cut-off with healing failure. We further explored the type of amputation conducted for its effect on heterogeneity using sensitivity analyses. For each cut-off, we compared the pooled summary estimate of prospective cohort studies that reported the occurrence of amputation revision with the estimate derived from an analysis of only those studies that evaluated patients with BKA or AKA. Differences were assessed using the χ^2 test with a p-value of 0.05 being considered significant.

Results

Description of studies

Of the 992 articles identified in the literature search, 31 met the inclusion criteria.[25–55] A summary of the study selection can be found in Fig. 1. Only one of these articles[42] undertook a multivariable analysis to assess $TcPO_2$ as an independent predictor.

The 31 studies that met the inclusion criteria for this review were of various designs and focussed on slightly different research questions. Table 1 summarises the general characteristics of these studies. Of the 26 observational studies, 21 were prospective cohort studies while five were retrospective chart reviews. The remaining five studies,[29,30,39,42,49] were designed as clinical trials, assessing the use of $TcPO_2$ as a method for selecting lower limb amputation levels, with one exception; Butler et al.[29] focussed on the role of supplemental oxygen therapy in lower limb amputation healing with secondary analyses that addressed our review question. Only patients from the control group of this trial were included in our review.

In the 31 studies included in this review, a total of 1824 patients with 1960 amputations were evaluated with $TcPO_2$. Indications for lower limb amputation were largely similar across all the studies and included: peripheral vascular disease, occlusive arterial disease, non-healing ischaemic ulcers, infection, gangrene and rest pain. Only one study[55] focussed solely on patients with diabetes mellitus.

Study quality assessment

A summary of the study quality assessment can be found in Table 2. The majority of the studies included in this review were of

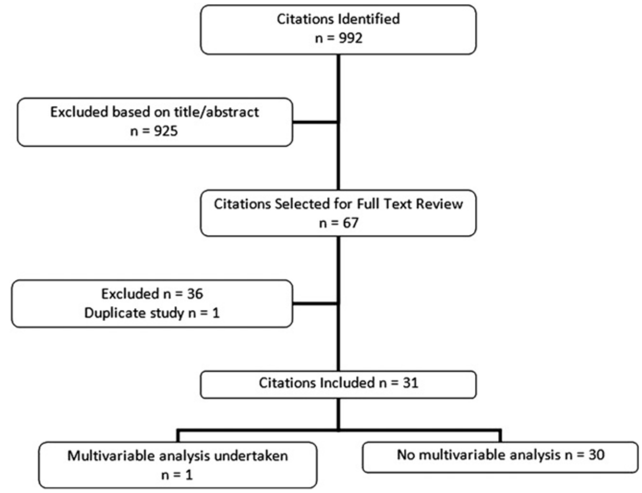

Figure 1. PRISMA flow diagram.

single-centre observational design and approached all patients reporting to the centre with non-healing ulcers, severe leg ischaemia or those that were scheduled for lower limb amputations. Only two of the studies further described exclusion criteria that would minimise the effect of confounders such as ipsilateral knee joint disease in BKAs[29] or other handicaps.[31] Two patients in the study by Andrews et al.[26] were lost to follow-up. None of the other studies reported any patients lost to follow-up.

Only six studies[27,30,35,41,47,50] stated specifically that they blinded the surgeons who selected the amputation level to the results of the $TcPO_2$ measurements. No studies reported blinding of the outcome assessor. However, as many of the studies considered re-amputation their end point, this is unlikely to have been a significant source of bias.

A major concern in the 10 studies that did not use re-amputation as the end point was the lack of objectivity in their definition of their primary outcome. Only two of these studies[40,55] clearly defined how healing was assessed.

Study results

Keyzer-Dekker et al.[42] was the only study to analyse $TcPO_2$ as an independent predictor of amputation stump healing failure using multivariable analysis. They defined their end point as occurrence of re-amputation during a 1-year follow-up which occurred in 15 of the 52 participants (28.8%). The multivariable analysis adjusted for the type of amputation, the presence of gangrene, phantom or rest pain, acute ischaemia, vascular disease and diabetes mellitus. An adjusted odds ratio for the association between a preoperative $TcPO_2$ level below 20 mmHg and occurrence of re-amputation was calculated to be 3.08 (95% confidence interval (CI) 1.19–7.98; $p = 0.021$).

Two studies[49,54] only communicated their results descriptively. In each of these, the authors suggested that there was a correlation between low $TcPO_2$ values and amputation stump healing complication. These authors were contacted to provide further clarification or data. Wyss et al.[54] responded that the primary data were no longer available. Two studies[25,39] performed lower limb amputations at the level where $TcPO_2$ was 24 or 30 mmHg, respectively. Healing failure occurred in 3 of 38 (7.9%) of amputations in Ameli et al.[25] and 2 of 20 (10.0%) amputations in Ito et al.[39]

Nineteen of the studies in this review, representing 1212 patients with 1280 amputations, reported the results of a

Table 1
Description of studies included in review.

Study	Design	Sample size	Endpoint outcome	Events (%)	*p*-value[a]
Ameli, 1989	Clinical trial	38	Primary healing failure (not defined)	3 (7.9)	–
Andrews, 2010	Restrospective cohort/chart review	371	Amputation revision to a more proximal level	95 (25.5)	<0.05
Bacharach, 1992	Retrospective cohort/chart review	75 (90 amputations)	Amputation revision to a more proximal level	21 (23.3)	<0.001
Bunt, 1996	Prospective cohort	103 (133 amputations)	Healing failure (not defined)	27 (20.3)	<0.05
Burgess, 1982	Prospective cohort	37	Amputation revision	7 (18.9)	<0.01
Butler, 1987	Clinical trial	22	Amputation revision	10 (25.6)	<0.005
Casillas, 1993	Retrospective cohort/chart review	43 (46 amputations)	Prosthetic fitting score, Amputation revision to a more proximal level	4 (8.7)	–
Chambon, 1992	Prospective cohort	33 (36 amputations)	Healing failure (not defined)	10 (27.8)	0.05
Christensen, 1986	Prospective cohort	42	Amputation revision	5 (11.9)	<0.002
Depairon, 1986	Prospective cohort	34 (35 amputations)	Amputation revision	5 (14.3)	–
Dowd, 1986	Prospective cohort	51	Healing failure (not defined)	9 (17.6)	–
Falstie-Jense, 1989	Retrospective cohort/chart review	72 (74 amputations)	Healing failure (not defined)	15 (20.3)	NS
Harward, 1985	Prospective cohort	101 (119 amputations)	Amputation revision	20 (16.8)	–
Hauser, 1987	Prospective cohort	66	Healing failure (not defined)	21 (31.8)	<0.001
Ito, 1984	Clinical trial	29 (31 amputations)	Healing failure (not defined)	3 (9.7)	–
Karanfilian, 1986	Prospective cohort	20	Open or nonviable wound edges; Signs of infection	2 (10.0)	<0.05
Katsamouris, 1984	Prospective cohort	29	Necrosis or breakdown of the initial amputation site without evidence of secondary healing, requiring amputation revision to higher level	5 (17.2)	Anterior measurement: <0.02 Posterior measurement: <0.0001
Keyzer-Dekker, 2006	Clinical trial	52	Amputation revision to a more proximal level	15 (28.8)	–
Kram, 1989	Prospective cohort	40	Amputation revision to a more proximal level	7 (17.5)	<0.01
Misuri, 2000	Prospective cohort	20 (30 amputations)	Amputation revision	13 (43.3)	0.0004
Mustapha, 1983	Prospective cohort	14	Healing failure (not defined)	5 (35.7)	<0.001
Pinzur, 1992	Prospective cohort	38	Amputation revision to a more proximal level	6 (15.8)	–
Poredos, 2005	Prospective cohort	56	Amputation revision to a more proximal level	17 (30.4)	<0.01
Ratliff, 1984	Prospective cohort	59 (62 amputations)	Need for further surgical procedure, including amputation revision to a more proximal level	15 (24.2)	Above-knee measurement: <0.001 Below-knee measurement: <0.02
Rhodes, 1985	Clinical trial	12	Amputation revision to a more proximal level	1 (8.3)	–
Slagsvold, 1989	Prospective cohort	25	Amputation revision to a more proximal level	3 (12.0)	–
Szala, 1988	Prospective cohort	27	Amputation revision	7 (25.9)	–
Wagner, 1988	Prospective cohort	109 (66 BKAs)	Amputation revision or significant debridement	13 (12.6)	AKA with thigh measurement: >0.05 AKA with calf measurement: >0.05 BKA with thigh measurement: 0.035 BKA with calf measurement: <0.001
White, 1982	Prospective cohort	9	Amputation revision	3 (33.3)	<0.01
Wyss, 1988	Prospective cohort	162 (206 amputations)	Amputation revision	35 (17.0)	–
Zgonis, 2005	Retrospective cohort/chart review	35 (40 amputations)	Presence of ulcer at the site of amputation or amputation revision	12 (30.0)	<0.01

[a] For difference between mean $TcPO_2$ level of patients with events and those without using univariable analysis.

univariable association through Student's *t*-test or the Mann–Whitney *U* test. Eighteen studies[26–30,32,33,38,40,41,43–45,47,48,52,53,55] demonstrated a significant difference between the mean $TcPO_2$ levels of the healed and non-healed groups, as defined by a *p*-value of less than 0.05. Only one study[36] showed no significant difference.

The remaining seven studies[31,34,35,37,46,50,51] did not report a univariable association between $TcPO_2$ levels and lower limb amputation healing complications, but presented data that allowed for the calculation of an unadjusted RR of lower limb amputation healing complication associated with a $TcPO_2$ level below a cut-off of 10, 20, 30 or 40 mmHg.

Meta-analysis

A total of 23 studies[26–31,33–37,40–44,46–48,50–53] presented data that allowed for the calculation of an unadjusted RR of lower limb amputation healing complication associated with a $TcPO_2$ level below a cut-off of 10, 20, 30 or 40 mmHg. It was originally planned to pool the results of all of these studies; however, due to substantial heterogeneity, this analysis was deemed inappropriate. Instead, a meta-analysis was undertaken on the 14 prospective cohort studies that reported the occurrence of amputation revision.[28,33,34,37,41,43,44,46–48,50–53] These studies included 626 patients with 658 amputations. Forest plots displaying the results of the pooled analysis for each cut-off value are displayed in Figs. 2–5. Based on 11 studies, a $TcPO_2$ value less than 10 mmHg displayed the strongest association with healing complication (RR 1.80, 95% CI 1.19–2.72). The 20-mmHg subgroup included all 14 of the studies and resulted in a pooled RR of 1.75 (95% CI 1.27–2.40). Cut-offs of 30 mmHg and 40 mmHg displayed pooled RRs of 1.41 (95% CI 1.22–1.62) and 1.24 (95% CI 1.13–1.39), respectively. The pooled RRs for all four subgroups were statistically significant.

Heterogeneity

Substantial heterogeneity was observed in the 20-mmHg cut-off analysis ($I^2 = 68\%$). Heterogeneity in the 10, 30 and 40 mmHg accounted for 47%, 44% and 22% of the variation between studies,

Table 2
Study quality assessment.

Study	Method of sample selection	Number of patients lost to follow-up	Blinding	Standardization of healing assessment method
Ameli, 1989	Consecutive patients	None reported	No blinding reported	No
Andrews, 2010	Retrospective selection from a surgical database	Two	No blinding reported	Yes
Bacharach, 1992	Retrospective selection from patient records	None reported	Surgeons blinded	Yes
Bunt, 1996	Consecutive patients	None reported	Surgeons blinded	No
Burgess, 1982	Consecutive patients	None reported	No blinding reported	Yes
Butler, 1987	Consecutive patients, controlling for ipsilateral knee joint disease	None reported	No blinding reported	Yes
Casillas, 1993	Retrospective selection from patient records, controlling for ambulatory handicaps	None reported	No blinding reported	Yes
Chambon, 1992	Consecutive patients	None reported	No blinding reported	No
Christensen, 1986	Consecutive patients	None reported	No blinding reported	Yes
Depairon, 1986	Consecutive patients	None reported	No blinding reported	Yes
Dowd, 1986	Consecutive patients	None reported	Surgeons blinded	No
Falstie-Jense, 1989	Retrospective selection from patient records	None reported	No blinding reported	No
Harward, 1985	Consecutive patients	None reported	No blinding reported	Yes
Hauser, 1987	Consecutive patients	None reported	No blinding reported	No
Ito, 1984	Consecutive patients	None reported	No blinding reported	No
Karanfilian, 1986	Consecutive patients	None reported	No blinding reported	Yes
Katsamouris, 1984	Consecutive patients	None reported	Surgeons blinded	Yes
Keyzer-Dekker, 2006	Consecutive patients	None reported	No blinding reported	Yes
Kram, 1989	Consecutive patients	None reported	No blinding reported	Yes
Misuri, 2000	Consecutive patients	None reported	No blinding reported	Yes
Mustapha, 1983	Consecutive patients	None reported	No blinding reported	No
Pinzur, 1992	Consecutive patients	None reported	No blinding reported	Yes
Poredos, 2005	Consecutive patients	None reported	Surgeons blinded	Yes
Ratliff, 1984	Consecutive patients	None reported	No blinding reported	Yes
Rhodes, 1985	Consecutive patients	None reported	No blinding reported	Yes
Slagsvold, 1989	Consecutive patients	None reported	Surgeons blinded	Yes
Szala, 1988	Consecutive patients	None reported	No blinding reported	Yes
Wagner, 1988	Consecutive patients	None reported	No blinding reported	Yes
White, 1982	Consecutive patients	None reported	No blinding reported	Yes
Wyss, 1988	Consecutive patients	None reported	No blinding reported	Yes
Zgonis, 2005	Retrospective selection from patient records	None reported	No blinding reported	Yes

respectively. There were statistically significant differences between the effect estimates at a cut-off of 20 mmHg when compared to 40 mmHg ($p = 0.04$) and borderline statistically significant differences between the effect estimates at 10 mmHg and 40 mmHg ($p = 0.08$), but not when comparing the other cut-off values. In the meta-regression analysis, neither year of publication nor length of follow-up explained the heterogeneity found.

Sensitivity analyses using only prospective cohort studies that evaluated BKAs and AKAs and that defined their end point outcome as the occurrence of amputation revision for each cut-off value demonstrated a reduction in the proportion of variation explained by heterogeneity between studies (Table 3). These analyses were associated with pooled RRs further from 1.00 for all of the cut-off values, though these differences were not statistically significant.

Discussion

Clinical implications

The studies summarised in this review suggest an association between low $TcPO_2$ values and healing failure of the lower limb amputation stump. Pooling of unadjusted summary estimates from 14 prospective cohort studies demonstrated a significant

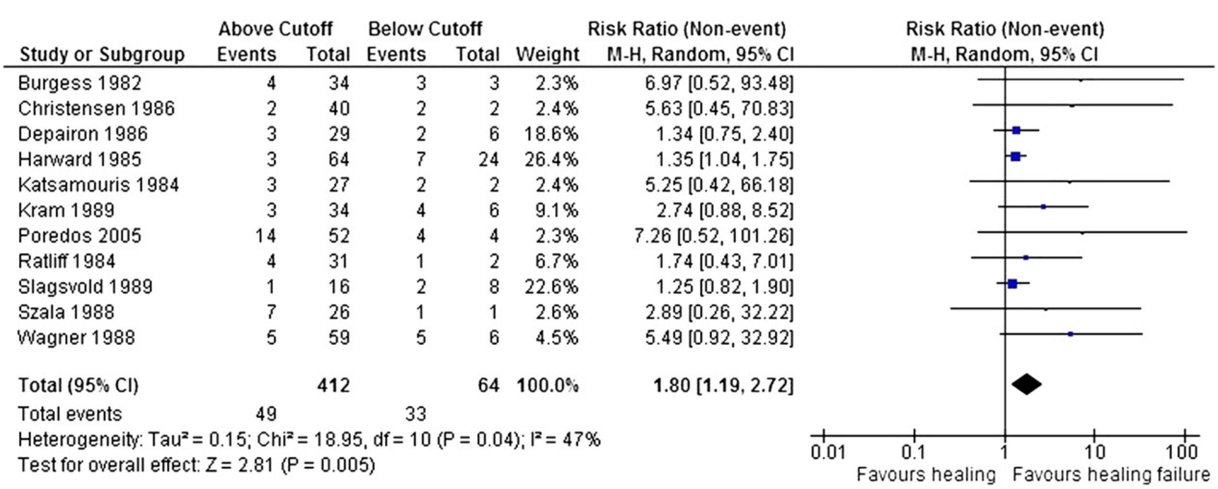

Figure 2. Forest plot of unadjusted risk of lower limb amputation healing failure associated with preoperative $TcPO_2$ level below 10 mmHg.

Study or Subgroup	Above Cutoff Events	Above Cutoff Total	Below Cutoff Events	Below Cutoff Total	Weight	Risk Ratio (Non-event) M-H, Random, 95% CI
Burgess 1982	3	33	4	4	1.3%	8.97 [0.65, 124.71]
Christensen 1986	1	38	4	4	1.3%	9.62 [0.69, 133.44]
Depairon 1986	1	19	4	16	13.6%	1.26 [0.93, 1.71]
Harward 1985	1	48	9	40	14.9%	1.26 [1.06, 1.50]
Katsamouris 1984	3	27	2	2	1.4%	5.25 [0.42, 66.18]
Kram 1989	1	28	6	12	10.3%	1.93 [1.09, 3.41]
Misuri 2000	2	17	11	13	4.4%	5.74 [1.58, 20.76]
Pinzur 1992	4	34	2	4	6.2%	1.76 [0.66, 4.74]
Poredos 2005	8	39	10	17	10.1%	1.93 [1.07, 3.48]
Ratliff 1984	4	30	1	3	7.7%	1.30 [0.58, 2.93]
Slagsvold 1989	1	15	2	9	12.8%	1.20 [0.83, 1.75]
Szala 1988	3	22	5	5	1.3%	10.17 [0.71, 145.37]
Wagner 1988	3	54	7	11	8.0%	2.60 [1.19, 5.69]
White 1982	1	4	2	5	6.8%	1.25 [0.50, 3.11]
Total (95% CI)		**408**		**145**	**100.0%**	**1.75 [1.27, 2.40]**
Total events	36		69			

Heterogeneity: Tau² = 0.17; Chi² = 41.18, df = 13 (P < 0.0001); I² = 68%
Test for overall effect: Z = 3.46 (P = 0.0005)

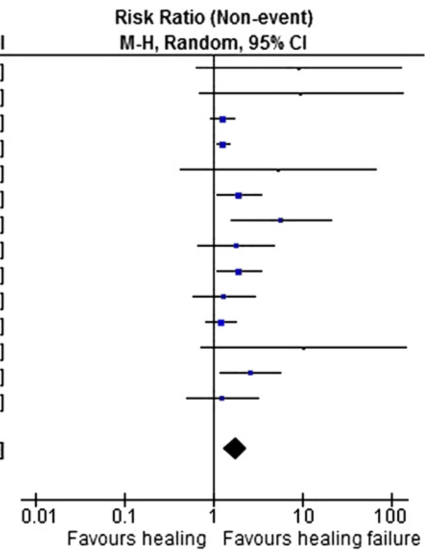

Figure 3. Forest plot of unadjusted risk of lower limb amputation healing failure associated with preoperative $TcPO_2$ level below 20 mmHg.

association between risk of lower limb amputation healing failure leading to amputation revision and a $TcPO_2$ level below cut-offs of 10–40 mmHg. The RR of lower limb amputation healing failure for patients with a $TcPO_2$ value below a cut-off appears to decrease with increasing cut-off values. This inverse relationship supports a graded effect of evaluated cut-off values on risk and is in the direction we hypothesised.

The use of $TcPO_2$ in addition to the clinical examination in determining an appropriate level for amputation selection may be warranted, but its independent predictive value has not been determined. Furthermore, a cut-off value below which healing failure is likely has not been optimally defined. Nevertheless, $TcPO_2$ is a promising tool and its adoption may significantly assist in the surgical and clinical care of this patient population by providing clinicians with a means to assess appropriate lower limb amputation levels. This will hopefully prevent amputations at inappropriate levels and thus subsequent amputation revisions, as well as possibly identifying patients who will heal at a more distal level. More distal amputations have been shown to be associated with reduced mortality and improved quality of life – this is an important clinical goal.

Limitations

This review was limited by the low number of studies reporting a multivariable association between $TcPO_2$ levels and amputation stump healing complications. Despite using a sensitive search strategy without language restrictions in five relevant electronic databases and hand-searches of reference lists and relative reviews, only one such study was retrieved. Without further research, the independent predictive ability of $TcPO_2$, and thus its usefulness in clinical practice, cannot be properly assessed.

Our meta-regression demonstrated that $TcPO_2$ cut-off values, year of publication and length of follow-up could not explain all of the heterogeneity in this analysis. Despite controlling for variability in study design and methods of assessing healing of the amputation stump, there was significant heterogeneity in the analysis of a 20-mmHg cut-off. A sensitivity analysis on the type of amputation studied did lead to a reduction in heterogeneity in each analysis. However, it did not result in a significant change in the pooled summary estimate for any cut-off value. Our *a priori* hypothesis regarding heterogeneity also included variability in study validity, patient characteristics and methods of measuring

Study or Subgroup	Above Cutoff Events	Above Cutoff Total	Below Cutoff Events	Below Cutoff Total	Weight	Risk Ratio (Non-event) M-H, Random, 95% CI
Burgess 1982	2	30	5	7	1.4%	3.27 [1.01, 10.58]
Christensen 1986	1	31	4	11	6.8%	1.52 [0.97, 2.39]
Depairon 1986	1	17	4	18	12.0%	1.21 [0.92, 1.59]
Harward 1985	0	32	10	56	18.3%	1.21 [1.06, 1.38]
Katsamouris 1984	2	28	3	3	0.3%	7.31 [0.55, 97.95]
Kram 1989	0	22	7	18	8.8%	1.62 [1.12, 2.34]
Pinzur 1992	2	26	4	12	7.6%	1.38 [0.91, 2.10]
Poredos 2005	2	22	16	34	9.6%	1.72 [1.22, 2.42]
Ratliff 1984	1	20	4	13	8.6%	1.37 [0.94, 2.00]
Slagsvold 1989	0	10	3	14	10.8%	1.25 [0.92, 1.69]
Szala 1988	1	17	7	10	2.0%	3.14 [1.21, 8.15]
Wagner 1988	2	40	8	25	11.8%	1.40 [1.06, 1.85]
White 1982	1	3	2	6	1.9%	1.00 [0.38, 2.66]
Total (95% CI)		**298**		**227**	**100.0%**	**1.41 [1.22, 1.62]**
Total events	15		77			

Heterogeneity: Tau² = 0.02; Chi² = 21.41, df = 12 (P = 0.04); I² = 44%
Test for overall effect: Z = 4.69 (P < 0.00001)

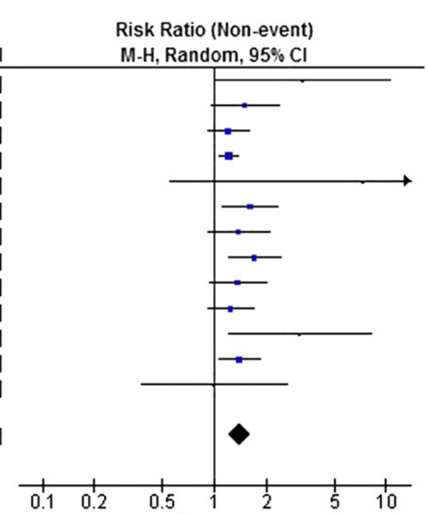

Figure 4. Forest plot of unadjusted risk of lower limb amputation healing failure associated with preoperative $TcPO_2$ level below a 30 mmHg.

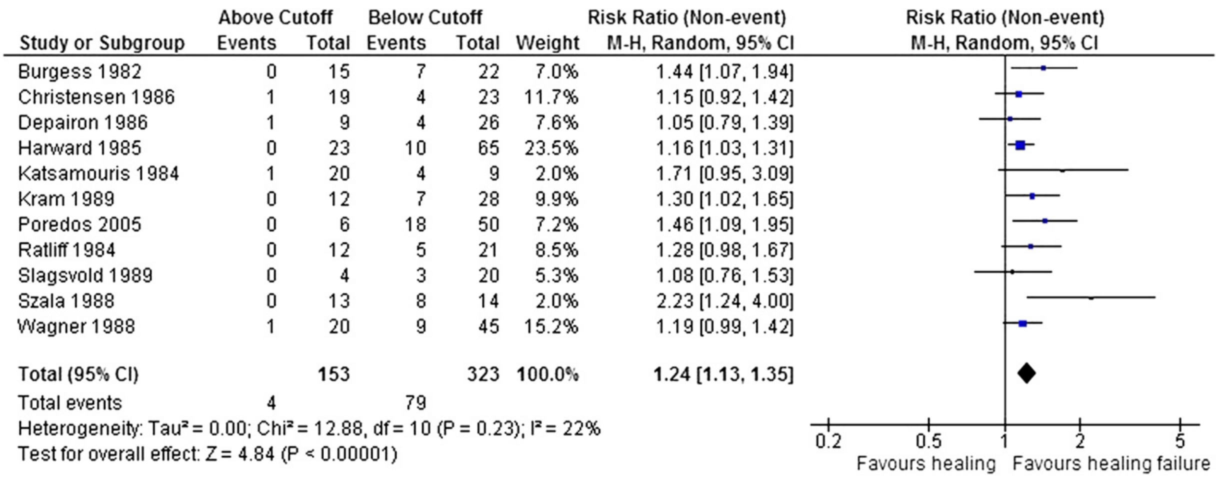

Figure 5. Forest plot of unadjusted risk of lower limb amputation healing failure associated with preoperative $TcPO_2$ level below 40 mmHg.

Table 3
Sensitivity analyses.

Cut-off value (mmHg)	Meta-analysis	Sensitivity analysis	p-value[a]
10	RR 1.80 (95% CI 1.19–2.72) $I^2 = 47\%$	RR 3.29 (95% CI 1.64–6.61) $I^2 = 0\%$	0.15
20	RR 1.75 (95% CI 1.27–2.40) $I^2 = 68\%$	RR 2.01 (95% CI 1.41–2.44) $I^2 = 9\%$	0.56
30	RR 1.41 (95% CI 1.22–1.62) $I^2 = 44\%$	RR 1.53 (95% CI 1.31–1.79) $I^2 = 0\%$	0.44
40	RR 1.24 (95% CI 1.13–1.35) $I^2 = 22\%$	RR 1.26 (95% CI 1.14–1.39) $I^2 = 0\%$	0.77

[a] For difference between summary estimates with the studies pooled in the meta-analysis and with the sensitivity analysis, assessed using the χ^2 test.

$TcPO_2$. However, not enough data were available from the included studies to assess these variables in the meta-regression or sensitivity analyses. These sources of heterogeneity must be evaluated when considering applying the results of this meta-analysis to individual patients.

Finally, the studies included in this review were generally small and had methodological limitations including a lack of blinding and subjective assessment of healing failure of the amputation stump which may have introduced bias.

Conclusions

This review suggests that there is a positive and statistically significant association between $TcPO_2$ values below a cut-off level and healing complications of lower limb amputations. There is, however, insufficient evidence to judge whether this tool adds important information to clinical examination. Furthermore, a cut-off point at which this tool would perform optimally has not been determined. A large, sufficiently powered study that uses multivariable analysis is needed to guide clinical practice and future research.

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Conflict of Interest Statement

The authors do not declare any conflicts of interest.

Appendix. Supplementary material

Supplementary data related to this article can be found online at doi:10.1016/j.ejvs.2011.12.004.

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